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Concerns about safety of long acting beta-agonists for asthma - they think it's all over

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At last we can now apparently relax in the secure knowledge that long acting beta-agonists (LABA) are safe to use in persistent asthma when given in combination with inhaled corticosteroid (ICS), on the basis of the FDA mandated studies with either fluticasone/salmeterol or budesonide/formoterol which showed no increase in serious asthma related events while both combinations reduced exacerbations compared to ICS alone^{1,2}. Does this mean we can now prescribe ICS/LABA combination inhalers with impunity at step 3 and above of asthma guidelines?

The tenet of asthma therapy is to suppress the underlying inflammatory cascade from the top with ICS, which in turn attenuates downstream airway smooth muscle twitchiness, resulting in reduced reliever requirement (Figure). LABA act primarily on the bottom of the cascade but do not address the underlying inflammatory process. The therapeutic conundrum here is that using LABA alone may worsen control and only become safe when used in conjunction with ICS. LABA are potentially pro-inflammatory ligands acting via non-canonical G protein cyclic adenosine monophosphate (Gs-cAMP) independent pathways involving extracellular signal regulated kinases and beta-arrestin³. For example in antigen sensitized mice who were depleted of endogenous adrenaline, exposure to exogenous formoterol resulted in restoration of the asthma inflammatory phenotype⁴. Presumably the salutary effects of ICS mitigates the potential pro-inflammatory activity and associated adverse effects of LABA.

LABA may also act via canonical Gs-cAMP pathways on airway inflammatory cells to inhibit mediator release and reduce extravascular protein leakage.

Tolerance rapidly develops to LABA for their canonical effects on

inflammatory and smooth muscle cells as a consequence of adaptive beta-2 receptor down regulation and uncoupling of Gs-cAMP, due to prolonged receptor occupancy. This explains why chronic dosing with ICS/LABA results in predictable loss of protection against bronchoconstrictor stimuli⁵. Moreover there is cross tolerance between LABA and response to salbutamol resulting in a blunted reliever response. However a high dose of intravenous corticosteroid rapidly reverses beta-2 receptor down regulation and associated tolerance in asthmatic patients receiving regular ICS/LABA⁶. Not all patients respond the same in that bronchoprotective tolerance with ICS/LABA is greater in approximately 60% of individuals who possess one or two copies of the arginine-16 beta-2 receptor polymorphism, being more pronounced with formoterol compared to salmeterol reflecting differences in intrinsic beta-2 receptor activity⁷. In asthmatic children taking ICS/LABA the risk of an asthma exacerbation is increased by 1.52 fold in relation to each copy of the arginine allele⁸. The 15 % of individuals who have the homozygous arginine-16 genotype fare better with fluticasone plus montelukast compared with fluticasone plus salmeterol, making a cogent case for a more personalised therapy approach⁹. However, in asthmatic adults there was no difference between homozygous arginine/glycine-16 genotypes for effects of fluticasone/salmeterol on pulmonary function¹⁰.

So where does that leave us moving forwards with respect to using ICS/LABA to achieve optimal asthma control? It is likely that reduced exacerbations with LABA are due to stabilization of airway smooth muscle and improved airway geometry as they seem to be devoid of any clinically meaningful in vivo anti-inflammatory activity. Consequently patients who exhibit features of persistent

asthmatic inflammation such as raised exhaled breath nitric oxide, blood eosinophilia, or persistent airway hyperreactivity should have the dose and delivery of ICS optimised either alone or in combination with LABA. In support of this therapeutic strategy a higher dose of budesonide alone was found to be more effective in reducing severe exacerbations and suppressing eosinophils than a lower dose in conjunction with formoterol despite the latter producing better pulmonary function, while a higher dose of budesonide with formoterol was superior to both¹¹. It may not be possible to extrapolate from the somewhat artificial setting of a randomized controlled trial to what happens in real life. An observational study found that while adding LABA to ICS improved symptoms and reduced reliever requirements, using a higher ICS dose was more effective in reducing exacerbations and hospitalisations¹². However using concomitant ICS/LABA ab initio to improve symptoms may help to buy time and improve patient confidence while waiting for the ICS to start working.

An alternative approach is to use flexible dosing with ICS/LABA as single inhaler maintenance and reliever therapy (SMART) containing ICS and formoterol. Patients who are symptomatic receive extra doses of ICS every time they take formoterol as a reliever, so that they end up titrating their own anti-inflammatory therapy. This flexible approach results in patients only being temporarily exposed to higher ICS doses as for example when challenged by triggers such as virus or allergen. Compared to fixed dose ICS/LABA, using SMART reduces exacerbations along with lower overall ICS exposure. The SMART regimen effectively enforces the patient to adhere to ICS at least while they remain symptomatic, and also avoids the possibility of over reliance

on their salbutamol reliever while stopping their fixed dose ICS/LABA combination.

Perhaps it is somewhat premature to say that the ongoing controversy regarding the use of ICS/LABA is now all over. In particular, clinicians need to be vigilant to avoid over-prescribing of LABA and at the same time focus on suppressing the underlying inflammatory cascade.

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Figure Legend

The inflammatory cascade in asthma

The tenet of asthma therapy is to suppress the top of the inflammatory cascade resulting in downstream reduction of airway smooth muscle twitchiness thereby reducing reliever requirement. Since LABA only treat the bottom of the cascade to stabilize airway smooth muscle, anti-inflammatory therapy should be first optimized with ICS +/- LABA to achieve optimal control.

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